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A Five-Year Analysis of Botulinum Toxin Type A Injections: Some Unusual Features

ROBERT J. BALKAN, MD, AND TAYLOR POOLE, MD

We analyzed patients treated during the past five years with botulinum toxin type A for strabismus and blepharospasm, reviewed our successes, failures, and unusual cases, and drew conclusions based on these treatments. Thirty-seven percent of the strabismus patients were cured, but many patients who were outside the strict definitions, still believed that they were significantly improved. A prominent feature in the treatment of strabismus was variability. Frequently, patients expected to do poorly had encouraging results. One permanent overcorrection occurred, and it converted an esotopic patient into an exotropic one with diplopia. This has persisted for 2.5 years and is the longest reported overcorrection to our knowledge. Our results indicate that larger doses of botulinum toxin produce longer spasm-free intervals in the treatment of blepharospasm. One patient receiving injections for her blepharospasm discovered that its cause was her sedative medication. This is the first reported case of a benzodiazepine inducing blepharospasm to our knowledge.

Botulinum toxin type A is a potent neurotoxin which blocks the release of acetylcholine at the neuromuscular junction. Under the guidance of Alan Scott at the Smith Kettlewell Eye Research Foundation, a number of investigators have used this potent substance medically to alleviate blepharospasm and facial spasm[1-5] and reduce strabismic misalignment.[6-11]

Botulinum toxin has been used in many ophthalmologic maladies: to prevent contracture of an antagonist muscle after paralysis of the third or sixth cranial nerve,[9,12,13] to reduce basic strabismus,[6-11] to treat Graves's strabismic misalignment,[14] to reduce surgical overcorrections after muscle surgery[15-17] to reduce residual accommodative esotropic misalignment, to treat corneal exposure and entropion, to treat acquired nystagmus,[16] to treat blepharospasm with or without Meige syndrome,[1,2] and in the treatment of facial spasm.[3-5]

The rationale for using botulinum toxin in strabismus and blepharospasm has been previously reported by others.[18] We will review the treatment of strabismus, blepharospasm, and facial spasm patients over a five-year period in a private practice setting. Unusual features, complications, and interesting case histories will be described and compared with the results of others.

From the Department of Ophthalmology, Eye, Ear, Nose & Throat Hospital, and the Tulane Medical Center, New Orleans.
Address for reprints: Robert J. Balkan, MD, Dept. of Ophthalmology, Eye, Ear, Nose & Throat Hospital, 2626 Napoleon Ave., New Orleans, LA 70115.

Patients and Methods

After careful discussion and informed consent, patients were enrolled into the botulinum study, as outlined in the Protocol by Alan Scott. All injections were done by one author. Thirty strabismus patients have been enrolled. In patients with adequate fixation, cover–uncover measurements were used. In those with poor vision, a Krimsky measurement was used. Careful attention was paid to muscle restrictions, oblique dysfunction, and poor or weakened antagonists. Histories were noted, recording any previous strabismus operations.

Strabismus patients were given several drops of tetracaine and the site to be injected was further anesthetized with a tetracaine-soaked pledget held directly against the muscle insertion. A monopolar recording needle was used to provide specific electromyographic guidance into the muscle belly approaching the neuromuscular junction. The botulinum toxin was diluted so that, regardless of the dose, a bolus of 0.1mL could be injected. Further details concerning the injection techniques have been outlined elsewhere.[11] Strabismic measurements were done after two weeks and at a later time when the toxin had dissipated. The mean postoperative follow-up time was 11.5 months (range, 3–48 months). Many of these patients came from a distance. Hence the last postoperative measurement was used.

We injected 12 patients who had either blepharospasm, facial spasm, or blepharospasm with Meige syndrome. Each underwent a careful history, eye examination, and an occasional neurology referral. All blepharospasm patients received injections in at least four sites per eye: in the temporal and nasal upper lid and in the temporal and nasal lower lid. Usually, a brow and lateral orbicularis site was also selected. These patients were evaluated for the durations between injections and for the occurrence of side effects.

Results

We injected 30 strabismic patients. The mean preoperative deviation was 37.6PD (range, 10–80PD). The mean postoperative deviation was 20.9PD (range, 0–70PD). The average improvement was 16.7PD (Table I). The average number of injections was 1.4 for all strabismic patients. No patient received more than three injections. Fourteen of the 30 strabismic patients were esotropic. Their mean preoperative deviation was 39.9PD (range, 15–80PD). The mean postoperative deviation was 26.4PD (range, 0–55PD). Sixteen patients were exotropic. Their mean preoperative de-

Table II Complications of Injection for Strabismus

Ptosis—37%
Paresis of an adjacent extraocular muscle—10%
Pain at the injection site—3.3%
Permanent overcorrection with diplopia—3.3%

Table III Complications of Injection for Blepharospasm

Ectropion—17%
Tearing—17%
Eyelid swelling—17%
Ptosis and diplopia—0%

Table I Efficiency of Botulinum Toxin for Strabismus

	All Strabismus Patients (n = 30)	Esotropic (n = 14)	Exotropic (n = 16)
Mean preoperative deviation	37.6 (r = 10–80)	39.9 (r = 15–80)	35.6 (r = 10–70)
Mean postoperative deviation	20.9 (r = 0–70)	26.4 (r = 0–55)	16.2 (r = 0–70)
% of Cure	37%	29%	44%

Average follow-up time was 11.5 months (range, 3–48 months); all measurements in prism diopters (PD); r = range; and cure is defined as less than 10PD residual after an average number of injections.

viation was 35.6PD (range, 10–70PD). The mean postoperative deviation was 16.2PD (range, 0–70PD). If we use "less than 10PD of residual deviation" to define cure, we could say that 44% of the exotropic and 29% of the esotropic patients were cured with botulinum toxin. Thirty-seven percent of the total group of strabismic patients would be considered cured using this strict definition. Complications of injection for strabismus treatment (Table II) included transient ptosis (37%), paresis of an adjacent extraocular muscle and the subsequent vertical deviation (10%), pain at the injection site (3%), and permanent overcorrection with diplopia (3%) (one patient).

We treated 12 patients with blepharospasm, facial spasm, and blepharospasm with Meige syndrome. On average these patients were followed for 22 months and received a mean of three injections each. All patients symptomatically improved with each injection; although, retreatment was necessary. The average dose used was 58 units (range, 40–76 units). The average interval between injections was 4.77 months. The complications of injection for blepharospasm included lid swelling (17%), ectropion (17%), and tearing (17%); there was no incidence of diplopia or ptosis (Table III).

Discussion

Often the response to botulinum toxin could be anticipated using parameters set forth by Lingua,[19] i.e., less success with large deviations, less success with restrictive disease or weak antagonists, or less success with poor early responses to the injection. Still, we found almost as many cases that contradicted these guidelines. Some of our best results (patients 17, 18, 21, 22, and 15) had fairly large-angle strabismus which responded surprisingly well to this treatment (Table IV).

Patient 18 is interesting because he had a 35PD sensory left exotropia due to a macular hole and dense cataract. After cataract extraction and epikeratophakia, the eye remained 35PD left exotropic. However, after one injection with botulinum toxin, the patient became orthophoric and has maintained this alignment for four years (Figures 1 and 2).

Some authors report that the stability of realignment with botulinum toxin is aided and dependent on binocular functions and fusion.[8,9] In case 18, the patient's peripheral fusion may have been responsible for maintaining alignment despite the central macular hole.

Figure 1. Preoperative deviation.

Figure 2. Postoperative deviation.

Challenging this necessity for binocular vision to produce good results, we present patient 25. She had a blind right eye with 45PD of right exotropia. Still, she achieved excellent alignment despite the complete absence of binocularity. In addition, she was hindered by marked oblique dysfunction. She had a sensory right exotropia of 45PD with 4 + superior oblique overactions OU. The right eye was markedly hypertropic when the left seeing eye fixated under the duress of the left superior oblique overaction. The right eye became hypotropic in left gaze. She had a 30PD reduction to 15PD of right exotropia seven months after her last botulinum injection. The referring physi-

Table IV Exotropic Patients

Patient No.	Type of Exotropia	Preoperative Injection Deviation	Postoperative Injection Deviation	Follow-up Time From Last Injection	No. of Injections	Restrictions, Weak Antagonist or Oblique Dysfunction	Complications	Muscle Injected	Dose or Average Dose (units)	Unusual Features
15	Consecutive XT after ET surgery	25 LXT	23 LXT	30 mons.	1	LIO overaction	Pain at injection site	LLR	5	
16	Sensory XT OS = LP	28 LXT	25 LXT	8 mons.	2	None	Ptosis	LLR	5.5	
17	Surgical over-correction	30 LXT	RET 6PD	3 mons.	1	Overcorrection of Jensen procedure	None	LLR	5	
18	Sensory XT	35 LXT	Orthophoria	48 mons.	1	None	Ptosis	LLR	5	Large effect
19	Consecutive XT after accom-modative ET	25 LXT 12 LT Hypotropia	20 LXT 12 Hypotropia	9 mons.	3	SO overaction	Ptosis	LLR	4.3	Elected surgery
20	Congenital third nerve	25 LXT	5 LXT	10 mons.	1	Had aberrant regeneration	None	LLR	5	
21	Old alternating	45 XT	Orthophoria	3 mons.	2	Overacting IOs	None	LLR	6	Lost to follow-up
22	RXT old	50 RXT	16 RXT	5 mons.	2	−2 adduction preoperative	None	RLR ×2	5.5	
23	Consecutive after ET surgery	25 LXT	25 LXT	3 mons.	2	None	Ptosis	LLR	7.5	Elected surgery
24	Sensory XT	70 LXT	70 LXT	3 mons.	1	Poor effect early	None	LLR	5	
25	Sensory XT Poor VA OD	45 RXT 20 R Hypertropia	15 RXT	7 mons.	2	Marked SO overaction	None	RLR	4.5	
26	Consecutive XT after ET surgery	10 LXT	10 LXT	5 mons.	1	None	None	LLR	2	
27	Sensory RXT	60 RXT	40 RXT	3 mons.	1	None	None	RLR	6	
28	Third nerve followed aneurysm	30 LXT 14 LHT	Orthophoria	3½ mons.	1	None	None	LLR	5	
29	Consecutive after ET surgery	30 XT	Orthophoria	6 mons.	1	Tight LR surgically induced	None	RLR	5	
30	RT third nerve	37 RXT 20 RHT	16 RXT 20 RHT	4 mons.	1	Weak RT MR	None	RLR	5	

R = right, L = left, ET = esotropia, XT = exotropia, MR = medial rectus, LR = lateral rectus, LP = light perception, VA = visual acuity, PD = prism diopters, IO = inferior oblique, SO = superior oblique.

Table V Esotropia Patients

Patient No.	Type of Esotropia	Preoperative Injection Deviation	Postoperative Injection Deviation	Follow-up Time From Last Injection	No. of Injections	Restrictions, Weak Antagonist or Oblique Dysfunction	Complications	Muscle Injected	Dose or Average Dose (units)	Unusual Features
1	Basic	18 RET	6 ET	4 mons.	1	None		RMR	4	
2	Residual accommodative	20 LET	4 LET	36 mons.	1	None	Hypertropia postoperative	LMR	2.5	
3	Infantile ET	30 LET	14 LET	6 mons.	1	None	Ptosis	LMR	5	
4	Infantile ET	55 LET	40 RET	8 mons.	1	Superior oblique overactions	None	RMR	5	
5	Old sixth nerve	50 RET	50 RET	6 mons.	1	Tight RMR Weak RLR	None			
6	Traumatic sixth nerve	80 RET	30 RET	3 mons.	1	Paretic RT LR	Paresis of inferior rectus	RMR	5	Eventually had surgery; unclear if effect would have held
7	Infantile ET	25 LET	20 LET	36 mons.	2		Ptosis	LMR	4.5	
8	Secondary ET	35 LET	14 LET	5 mons.	3	Tight LT MR Weak LT LR	Ptosis	LMR	6.3	Good effect given restriction
9	Infantile ET	30 LET	24 LET	21 mons.	2	A-pattern oblique overaction	Ptosis	LMR	4.5	
10	Infantile ET	30 LET or 15 RET	8 RXT or 7 LET	23 mons.	2	Multiple restrictions	Ptosis	LMR	6	Permanent overcorrection with diplopia
11	Old sixth nerve	55 LET	55 LET	5 mons.	1	Permanently weak RLR	Ptosis, hypertropia	LMR	5	
12	Bilateral sixth nerve secondary to multiple sclerosis	70 RET	55 RET	6 mons.	1	Bilaterally weak LR muscles	Ptosis for 2 mons.	RMR	5	
13	Residual accommodative ET	40 LET	25 LET	5 mons.	1	None	None	LMR		Angle kappa (looks good cosmetically)
14	Diabetic sixth nerve	20 LET	Orthophoria	5 mons.	1	Vertical restriction from old blow out. Required chin position to fuse	None	LMR	5	

R = right, L = left, ET = esotropia, XT = exotropia, MR = medial rectus, LR = lateral rectus.

cian noted that the alignment remained excellent two years later. The added bonus was the elimination of the right hypertropic deviation, since the right eye was lowered by its own superior oblique overaction, as it approached primary position.

Patient 10, who had a permanent overcorrection, is especially interesting and illustrates several points (Table V). Botulinum therapy has been considered less potent than surgery for strabismus correction. (Undercorrection is almost always the rule.) We are aware of only one report of a persistent overcorrection at six months.[11] Our patient started out with 30PD of esotropia and ended up with 8PD of exotropia. This young man, after several operations, had restrictive problems and very incomitant measurements. Preoperatively he fixed with the right eye and had 30PD of left esotropia. When fixing with his left eye, his right esotropia was only 15PD. Despite bilaterally tight medial recti which should have predicted a poor effect, he had a very pronounced effect. His left esotropia was reduced to 7PD two years after the last injection. Ironically, this patient switched fixation to his left eye and has had a persistent right exotropia and diplopia. To our knowledge this is only the second report of an overcorrection—and the longest persistence after the last injection.

Ptosis was common but usually slight and transient. Patient 10, however, had complete ptosis which took six months to resolve. This raises our usual worries about the inducement of amblyopia when treating children.

Botulinum toxin is a potent tool for rescuing surgical overcorrections. Both patient 26 and 29 were treated successfully for this problem. Patient 29 started out with 30PD of esotropia. After bilateral lateral rectus resections, he had 25PD of exotropia. At two weeks the overcorrection remained, and the left lateral rectus muscle was injected. This induced an excellent paresis, and after it resolved, the patient remained orthophoric. The overcorrection may have resolved spontaneously over time, but given our clinical experience, we doubt it. Botulinum toxin injection may be useful in reducing surgical overcorrections, if treated early.

Our experience treating the antagonist of paretic muscles was as expected, based on the results reported by others.[9-13] When the lesion was transient, the botulinum toxin prevented contracture of the antagonist and ensured eventual alignment.

Patient satisfaction is a separate issue and consideration. The term, cure, which is generally defined as less than 10PD of strabismic misalignment, may be misleading. For example, patient 9 had a positive angle kappa. Although we were only able to reduce her deviation from 30 to 24PD of left exotropia, she believed herself improved cosmetically. Similarly, patient 22 went from 50PD of right exo-

Table VI Blepharospasm and Facial Spasm Results

Patient No.	Follow-Up Time	No. of Injections	Average Interval Between Injections	Average Dose (Both Eyes)	Meige Features	Other Atypical Features	Complications
1	6 mons.	2	3 mons.	40	yes	no	no
2	24 mons.	3	7 mons.	75	no	no	no
3	40 mons.	4	6 mons.	70	yes	Dystonic movements due to triazolam	Lid swelling after injections
4	19 mons.	4	4½ mons.	55	no	no	no
5	6 mons.	2	3 mons.	50	yes	no	no
6	17 mons.	2	4 mons.	73	no	no	no
7	28 mons.	1	6 mons. before spasm resumed	76	no	S/P PKPs—didn't continue	no
8	36 mons.	4	5 mons.	65	no	no	Ectropion tearing
9	33 mons.	6	5 mons.	50	no	no	Ectropion
10	39 mons.	6	5 mons.	50	no	no	Lid swelling
11	12 mons.	1	Only one injection	42	no	no	no
12	6 mons.	1	4 mons. relief	40	no	Left facial spasm	no

S/P PKP = status post penetrating keratoplasty.

tropia to 16PD. Under strict criteria this would be considered a failure. The patient thought that his eyes were aligned perfectly. Hence, we believe that botulinum therapy is more useful than the strict definition of success or failure might indicate.

Our results show extreme variability in the effectiveness of botulinum toxin in treating strabismus. Often patients with relatively large angles of deviation and even restrictive components had surprisingly good results; some patients with minor deviations could not be helped.

The complications of ptosis and paralysis of an adjacent extraocular muscle were common but usually slight and transient. As noted, patient 10 had, however, complete ptosis for six months.

The treatment of blepharospasm patients with or without Meige syndrome and of facial spasm was successful. Some authors noted that the amount and duration of effect in treating blepharospasm was dose dependent;[1] others believe that there is no relationship.[11-15] Although our average dose of 58.73 units was higher than that used by other investigators,[2,3] it appears that the duration between our injections was also longer (4.7 months, Table VI).[1-4] Blepharospasm patient 3 was noteworthy because after four injections for severe blepharospasm and three years of follow-up, this patient claimed that all of her symptoms disappeared when she discontinued her sedative triazolam. After an examination, we concurred. Furthermore, when she resumed the medication, the symptoms recurred and again went away when she discontinued it. Presently, she is not receiving triazolam and is symptom free.

Dyskinetic movements have been reported after nasal decongestants, antihistamines, antiemetics, and anorectics.[20-23] Antipsychotic agents and neuroleptic agents have also been implicated in causing dyskinetic facial movements.[24-26] Joyce and co-worker[27] noted oral facial dyskinesia after an overdose of carbamazepine. As far as we are aware, this is the first case report in which a benzodiazepine has been documented as having caused blepharospasm.

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continued from page 324

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Affordable Automatic Lensmeter Gives Easy, Accurate Spectacle and Contact Lens Readings

Eye care professionals can now take readings for virtually any kind of lens easily and conveniently with a new automatic lensmeter from Nikon. The competitively priced NL-30 lensmeter requires little training, automatically recognizes left and right lenses, and can be used for all kinds of spectacle lenses, and hard and soft contacts. Designed for ease of use, the new lensmeter provides the same easy alignment as the best manual lensmeters but offers automated features like continuous diopter readings and right–left detection. A large, simple-to-read liquid crystal display makes it easy to see diopter and axis indications, and the word "OK" lights up when the lens is within alignment range. The display also indicates when the lens is centered precisely for markings.

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